

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Ashkenazi et al.

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For : SECRETED AND
TRANSMEMBRANE
POLYPEPTIDES AND NUCLEIC
ACIDS ENCODING THE SAME

Examiner : Hamud, Fozia M

Group Art Unit 1647

CERTIFICATE OF EXPRESS MAILING

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DECLARATION OF AVI ASHKENAZI, Ph.D UNDER 37 C.F.R. § 1.132

I, Avi Ashkenazi, Ph.D. declare and say as follows: -

1. I am Director and Staff Scientist at the Molecular Oncology Department of Genentech, Inc., South San Francisco, CA 94080.
2. I joined Genentech in 1988 as a postdoctoral fellow. Since then, I have investigated a variety of cellular signal transduction mechanisms, including apoptosis, and have developed technologies to modulate such mechanisms as a means of therapeutic intervention in cancer and autoimmune disease. I am currently involved in the investigation of a series of secreted proteins over-expressed in tumors, with the aim to identify useful targets for the development of therapeutic antibodies for cancer treatment.
3. My scientific Curriculum Vitae, including my list of publications, is attached to and forms part of this Declaration (Exhibit A).
4. Gene amplification is a process in which chromosomes undergo changes to contain multiple copies of certain genes that normally exist as a single copy, and is an important factor in the pathophysiology of cancer. Amplification of certain genes (e.g., Myc or Her2/Neu)

gives cancer cells a growth or survival advantage relative to normal cells, and might also provide a mechanism of tumor cell resistance to chemotherapy or radiotherapy.

5. If gene amplification results in over-expression of the mRNA and the corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach. Even in the absence of over-expression of the gene product, amplification of a cancer marker gene - as detected, for example, by the reverse transcriptase TaqMan® PCR or the fluorescence *in situ* hybridization (FISH) assays - is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy. An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

6. I understand that according to the Patent Office, absent data demonstrating that the increased copy number of a gene in certain types of cancer leads to increased expression of its product, gene amplification data are insufficient to provide substantial utility or well established utility for the gene product (the encoded polypeptide), or an antibody specifically binding the encoded polypeptide. However, even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so

made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By:

Avi Ashkenazi

Avi Ashkenazi, Ph.D.

Date:

9/15/03

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CURRICULUM VITAE

Avi Ashkenazi

July 2003

Personal:

Date of birth: 29 November, 1956
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Education:

1983: B.S. in Biochemistry, with honors, Hebrew University, Israel
1986: Ph.D. in Biochemistry, Hebrew University, Israel

Employment:

1983-1986: Teaching assistant, undergraduate level course in Biochemistry
1985-1986: Teaching assistant, graduate level course on Signal Transduction
1986 - 1988: Postdoctoral fellow, Hormone Research Dept., UCSF, and
Developmental Biology Dept., Genentech, Inc., with J. Ramachandran
1988 - 1989: Postdoctoral fellow, Molecular Biology Dept., Genentech, Inc.,
with D. Capon
1989 - 1993: Scientist, Molecular Biology Dept., Genentech, Inc.
1994 -1996: Senior Scientist, Molecular Oncology Dept., Genentech, Inc.
1996-1997: Senior Scientist and Interim director, Molecular Oncology Dept.,
Genentech, Inc.
1997-1990: Senior Scientist and preclinical project team leader, Genentech, Inc.
1999 -2002: Staff Scientist in Molecular Oncology, Genentech, Inc.
2002-present: Staff Scientist and Director in Molecular Oncology, Genentech, Inc.

Awards:

1988: First prize, The Boehringer Ingelheim Award

Editorial:

Editorial Board Member: Current Biology
Associate Editor, Clinical Cancer Research.
Associate Editor, Cancer Biology and Therapy.

Refereed papers:

1. Gertler, A., Ashkenazi, A., and Madar, Z. Binding sites for human growth hormone and ovine and bovine prolactins in the mammary gland and liver of the lactating cow. *Mol. Cell. Endocrinol.* **34**, 51-57 (1984).
2. Gertler, A., Shamay, A., Cohen, N., Ashkenazi, A., Friesen, H., Levanon, A., Gorecki, M., Aviv, H., Hadari, D., and Vogel, T. Inhibition of lactogenic activities of ovine prolactin and human growth hormone (hGH) by a novel form of a modified recombinant hGH. *Endocrinology* **118**, 720-726 (1986).
3. Ashkenazi, A., Madar, Z., and Gertler, A. Partial purification and characterization of bovine mammary gland prolactin receptor. *Mol. Cell. Endocrinol.* **50**, 79-87 (1987).
4. Ashkenazi, A., Pines, M., and Gertler, A. Down-regulation of lactogenic hormone receptors in Nb2 lymphoma cells by cholera toxin. *Biochemistry Internat.* **14**, 1065-1072 (1987).
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7. Peralta, E., Winslow, J., Peterson, G., Smith, D., Ashkenazi, A., Ramachandran, J., Schimerlik, M., and Capon, D. Primary structure and biochemical properties of an M2 muscarinic receptor. *Science* **236**, 600-605 (1987).
8. Peralta, E. Ashkenazi, A., Winslow, J., Smith, D., Ramachandran, J., and Capon, D. J. Distinct primary structures, ligand-binding properties and tissue-specific expression of four human muscarinic acetylcholine receptors. *EMBO J.* **6**, 3923-3929 (1987).
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10. Pines, M., Ashkenazi, A., Cohen-Chapnik, N., Binder, L., and Gertler, A. Inhibition of the proliferation of Nb2 lymphoma cells by femtomolar concentrations of cholera toxin and partial reversal of the effect by 12-o-tetradecanoyl-phorbol-13-acetate. *J. Cell. Biochem.* **37**, 119-129 (1988).
11. Peralta, E. Ashkenazi, A., Winslow, J., Ramachandran, J., and Capon, D. Differential regulation of PI hydrolysis and adenylyl cyclase by muscarinic receptor subtypes. *Nature* **334**, 434-437 (1988).
12. Ashkenazi, A., Peralta, E., Winslow, J., Ramachandran, J., and Capon, D. Functionally distinct G proteins couple different receptors to PI hydrolysis in the same cell. *Cell* **56**, 487-493 (1989).
13. Ashkenazi, A., Ramachandran, J., and Capon, D. Acetylcholine analogue stimulates DNA synthesis in brain-derived cells via specific muscarinic acetylcholine receptor subtypes. *Nature* **340**, 146-150 (1989).
14. Lammare, D., Ashkenazi, A., Fleury, S., Smith, D., Sekaly, R., and Capon, D. The MHC-binding and gp120-binding domains of CD4 are distinct and separable. *Science* **245**, 743-745 (1989).
15. Ashkenazi, A., Presta, L., Marsters, S., Camerato, T., Rosenthal, K., Fendly, B., and Capon, D. Mapping the CD4 binding site for human immunodeficiency virus type 1 by alanine-scanning mutagenesis. *Proc. Natl. Acad. Sci. USA* **87**, 7150-7154 (1990).
16. Chamow, S., Peers, D., Byrn, R., Mulkerrin, M., Harris, R., Wang, W., Bjorkman, P., Capon, D., and Ashkenazi, A. Enzymatic cleavage of a CD4 immunoadhesin generates crystallizable, biologically active Fd-like fragments. *Biochemistry* **29**, 9885-9891 (1990).
17. Ashkenazi, A., Smith, D., Marsters, S., Riddle, L., Gregory, T., Ho, D., and Capon, D. Resistance of primary isolates of human immunodeficiency virus type 1 to soluble CD4 is independent of CD4-rgp120 binding affinity. *Proc. Natl. Acad. Sci. USA* **88**, 7056-7060 (1991).
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21. Marsters, A., Frutkin, A., Simpson, N., Fendly, B. and Ashkenazi, A. Identification of cysteine-rich domains of the type 1 tumor necrosis receptor involved in ligand binding. *J. Biol. Chem.* **267**, 5747-5750 (1992).
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27. Chamow, S., Zhang, D., Tan, X., Mhtre, S., Marsters, S., Peers, D., Byrn, R., Ashkenazi, A., and Yunghans, R. A humanized bispecific immunoadhesin-antibody that retargets CD3+ effectors to kill HIV-1-infected cells. *J. Immunol.* **153**, 4268-4280 (1994).
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29. Haak-Frendscho, M., Marsters, S., Mordenti, J., Gillet, N., Chen, S., and Ashkenazi, A. Inhibition of TNF by a TNF receptor immunoadhesin: comparison with an anti-TNF mAb. *J. Immunol.* **152**, 1347-1353 (1994).

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42. Sheridan, J., Marsters, S., Pitti, R., Gurney, A., Skubatch, M., Baldwin, D., Ramakrishnan, L., Gray, C., Baker, K., Wood, W.I., Goddard, A., Godowski, P., and Ashkenazi, A. Control of TRAIL-induced apoptosis by a family of signaling and decoy receptors. *Science* 277, 818-821 (1997).

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53. Roth, W., Isenmann, S., Naumann, U., Kugler, S., Bahr, M., Dichgans, J., Ashkenazi, A., and Weller, M. Eradication of intracranial human malignant glioma xenografts by Apo2L/TRAIL. *Biochem. Biophys. Res. Commun.* **265**, 479-483 (1999).

54. Hymowitz, S.G., Christinger, H.W., Fuh, G., Ultsch, M., O'Connell, M., Kelley, R.F., Ashkenazi, A. and de Vos, A.M. Triggering Cell Death: The Crystal Structure of Apo2L/TRAIL in a Complex with Death Receptor 5. *Molec. Cell* **4**, 563-571 (1999).

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58. Yan, M., Marsters, S.A., Grewal, I.S., Wang, H., *Ashkenazi, A., and *Dixit, V.M. Identification of a receptor for BlyS demonstrates a crucial role in humoral immunity. *Nature Immunol.* **1**, 37-41 (2000).

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Review articles:

1. Ashkenazi, A., Peralta, E., Winslow, J., Ramachandran, J., and Capon, D., J. Functional role of muscarinic acetylcholine receptor subtype diversity. *Cold Spring Harbor Symposium on Quantitative Biology*. **LIII**, 263-272 (1988).
2. Ashkenazi, A., Peralta, E., Winslow, J., Ramachandran, J., and Capon, D. Functional diversity of muscarinic receptor subtypes in cellular signal transduction and growth. *Trends Pharmacol. Sci.* Dec Supplement, 12-21 (1989).
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4. Ashkenazi, A., Capon, and D. Ward, R. Immunoadhesins. *Int. Rev. Immunol.* **10**, 217-225 (1993).
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6. Krantz, S. B., Means, R. T., Jr., Lina, J., Marsters, S. A., and Ashkenazi, A. Inhibition of erythroid colony formation in vitro by gamma interferon. In *Molecular Biology of Hematopoiesis* (N. Abraham, R. Shadduck, A. Levine F. Takaku, eds.) Intercept Ltd. Paris, Vol. 3, p. 135-147 (1994).
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12. Ashkenazi, A., and Dixit, V. Apoptosis control by death and decoy receptors. *Curr. Opin. Cell. Biol.* **11**, 255-260 (1999).

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14. Ashkenazi, A. Targeting death and decoy receptors of the tumor necrosis factor superfamily. *Nature Rev. Cancer* 2, 420-430 (2002).
15. LeBlanc, H. and Ashkenazi, A. Apoptosis signaling by Apo2L/TRAIL. *Cell Death and Differentiation* 10, 66-75 (2003).
16. Almasan, A. and Ashkenazi, A. Apo2L/TRAIL: apoptosis signaling, biology, and potential for cancer therapy. *Cytokine and Growth Factor Reviews* 14, 337-348 (2003).

Book:

Antibody Fusion Proteins (Chamow, S., and Ashkenazi, A., eds., John Wiley and Sons Inc.) (1999).

Talks:

1. Resistance of primary HIV isolates to CD4 is independent of CD4-gp120 binding affinity. UCSD Symposium, HIV Disease: Pathogenesis and Therapy. Greenelefe, FL, March 1991.
2. Use of immuno-hybrids to extend the half-life of receptors. IBC conference on Biopharmaceutical Halflife Extension. New Orleans, LA, June 1992.
3. Results with TNF receptor Immunoadhesins for the Treatment of Sepsis. IBC conference on Endotoxemia and Sepsis. Philadelphia, PA, June 1992.
4. Immunoadhesins: an alternative to human antibodies. IBC conference on Antibody Engineering. San Diego, CA, December 1993.
5. Tumor necrosis factor receptor: a potential therapeutic for human septic shock. American Society for Microbiology Meeting, Atlanta, GA, May 1993.
6. Protective efficacy of TNF receptor immunoadhesin vs anti-TNF monoclonal antibody in a rat model for endotoxic shock. 5th International Congress on TNF. Asilomar, CA, May 1994.
7. Interferon- γ signals via a multisubunit receptor complex that contains two types of polypeptide chain. American Association of Immunologists Conference. San Francisco, CA, July 1995.
8. Immunoadhesins: Principles and Applications. Gordon Research Conference on Drug Delivery in Biology and Medicine. Ventura, CA, February 1996.

9. Apo-2 Ligand, a new member of the TNF family that induces apoptosis in tumor cells. Cambridge Symposium on TNF and Related Cytokines in Treatment of Cancer. Hilton-Head, NC, March 1996.
10. Induction of apoptosis by Apo2 Ligand. American Society for Biochemistry and Molecular Biology, Symposium on Growth Factors and Cytokine Receptors. New Orleans, LA, June, 1996.
11. Apo2 ligand, an extracellular trigger of apoptosis. 2nd Clontech Symposium, Palo Alto, CA, October 1996.
12. Regulation of apoptosis by members of the TNF ligand and receptor families. Stanford University School of Medicine, Palo Alto, CA, December 1996.
13. Apo-3: a novel receptor that regulates cell death and inflammation. 4th International Congress on Immune Consequences of Trauma, Shock, and Sepsis. Munich, Germany, March 1997.
14. New members of the TNF ligand and receptor families that regulate apoptosis, inflammation, and immunity. UCLA School of Medicine, LA, CA, March 1997.
15. Immunoadhesins: an alternative to monoclonal antibodies. 5th World Conference on Bispecific Antibodies. Volendam, Holland, June 1997.
16. Control of Apo2L signaling. Cold Spring Harbor Laboratory Symposium on Programmed Cell Death. Cold Spring Harbor, New York. September, 1997.
17. Chairman and speaker, Apoptosis Signaling session. IBC's 4th Annual Conference on Apoptosis. San Diego, CA., October 1997.
18. Control of Apo2L signaling by death and decoy receptors. American Association for the Advancement of Science. Philadelphia, PA, February 1998.
19. Apo2 ligand and its receptors. American Society of Immunologists. San Francisco, CA, April 1998.
20. Death receptors and ligands. 7th International TNF Congress. Cape Cod, MA, May 1998.
21. Apo2L as a potential therapeutic for cancer. UCLA School of Medicine. LA, CA, June 1998.
22. Apo2L as a potential therapeutic for cancer. Gordon Research Conference on Cancer Chemotherapy. New London, NH, July 1998.
23. Control of apoptosis by Apo2L. Endocrine Society Conference, Stevenson, WA, August 1998.
24. Control of apoptosis by Apo2L. International Cytokine Society Conference, Jerusalem, Israel, October 1998.

25. Apoptosis control by death and decoy receptors. American Association for Cancer Research Conference, Whistler, BC, Canada, March 1999.
26. Apoptosis control by death and decoy receptors. American Society for Biochemistry and Molecular Biology Conference, San Francisco, CA, May 1999.
27. Apoptosis control by death and decoy receptors. Gordon Research Conference on Apoptosis, New London, NH, June 1999.
28. Apoptosis control by death and decoy receptors. Arthritis Foundation Research Conference, Alexandria GA, Aug 1999.
29. Safety and anti-tumor activity of recombinant soluble Apo2L/TRAIL. Cold Spring Harbor Laboratory Symposium on Programmed Cell Death. Cold Spring Harbor, NY, September 1999.
30. The Apo2L/TRAIL system: therapeutic potential. American Association for Cancer Research, Lake Tahoe, NV, Feb 2000.
31. Apoptosis and cancer therapy. Stanford University School of Medicine, Stanford, CA, Mar 2000.
32. Apoptosis and cancer therapy. University of Pennsylvania School of Medicine, Philadelphia, PA, Apr 2000.
33. Apoptosis signaling by Apo2L/TRAIL. International Congress on TNF. Trondheim, Norway, May 2000.
34. The Apo2L/TRAIL system: therapeutic potential. Cap-CURE summit meeting. Santa Monica, CA, June 2000.
35. The Apo2L/TRAIL system: therapeutic potential. MD Anderson Cancer Center. Houston, TX, June 2000.
36. Apoptosis signaling by Apo2L/TRAIL. The Protein Society, 14th Symposium. San Diego, CA, August 2000.
37. Anti-tumor activity of Apo2L/TRAIL. AAPS annual meeting. Indianapolis, IN Aug 2000.
38. Apoptosis signaling and anti-cancer potential of Apo2L/TRAIL. Cancer Research Institute, UC San Francisco, CA, September 2000.
39. Apoptosis signaling by Apo2L/TRAIL. Kenote address, TNF family Minisymposium, NIH. Bethesda, MD, September 2000.
40. Death receptors: signaling and modulation. Keystone symposium on the Molecular basis of cancer. Taos, NM, Jan 2001.
41. Preclinical studies of Apo2L/TRAIL in cancer. Symposium on Targeted therapies in the treatment of lung cancer. Aspen, CO, Jan 2001.

42. Apoptosis signaling by Apo2L/TRAIL. Weizmann Institute of Science, Rehovot, Israel, March 2001.
43. Apo2L/TRAIL: Apoptosis signaling and potential for cancer therapy. Weizmann Institute of Science, Rehovot, Israel, March 2001.
44. Targeting death receptors in cancer with Apo2L/TRAIL. Cell Death and Disease conference, North Falmouth, MA, Jun 2001.
45. Targeting death receptors in cancer with Apo2L/TRAIL. Biotechnology Organization conference, San Diego, CA, Jun 2001.
46. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Gordon Research Conference on Apoptosis, Oxford, UK, July 2001.
47. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Cleveland Clinic Foundation, Cleveland, OH, Oct 2001.
48. Apoptosis signaling by death receptors: overview. International Society for Interferon and Cytokine Research conference, Cleveland, OH, Oct 2001.
49. Apoptosis signaling by death receptors. American Society of Nephrology Conference. San Francisco, CA, Oct 2001.
50. Targeting death receptors in cancer. Apoptosis: commercial opportunities. San Diego, CA, Apr 2002.
51. Apo2L/TRAIL signaling and apoptosis resistance mechanisms. Kimmel Cancer Research Center, Johns Hopkins University, Baltimore MD. May 2002.
52. Apoptosis control by Apo2L/TRAIL. (Keynote Address) University of Alabama Cancer Center Retreat, Birmingham, Ab. October 2002.
53. Apoptosis signaling by Apo2L/TRAIL. (Session co-chair) TNF international conference. San Diego, CA. October 2002.
54. Apoptosis signaling by Apo2L/TRAIL. Swiss Institute for Cancer Research (ISREC). Lausanne, Swizerland. Jan 2003.
55. Apoptosis induction with Apo2L/TRAIL. Conference on New Targets and Innovative Strategies in Cancer Treatment. Monte Carlo. February 2003.
56. Apoptosis signaling by Apo2L/TRAIL. Hermelin Brain Tumor Center Symposium on Apoptosis. Detroit, MI. April 2003.
57. Targeting apoptosis through death receptors. Sixth Annual Conference on Targeted Therapies in the Treatment of Breast Cancer. Kona, Hawaii. July 2003.
58. Targeting apoptosis through death receptors. Second International Conference on Targeted Cancer Therapy. Washington, DC. Aug 2003.

Issued Patents:

1. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,329,028 (Jul 12, 1994).
2. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,605,791 (Feb 25, 1997).
3. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 5,889,155 (Jul 27, 1999).
4. Ashkenazi, A., APO-2 Ligand. US patent 6,030,945 (Feb 29, 2000).
5. Ashkenazi, A., Chunthrapai, A., Kim, J., APO-2 ligand antibodies. US patent 6,046,048 (Apr 4, 2000).
6. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 6,124,435 (Sep 26, 2000).
7. Ashkenazi, A., Chunthrapai, A., Kim, J., Method for making monoclonal and cross-reactive antibodies. US patent 6,252,050 (Jun 26, 2001).
8. Ashkenazi, A. APO-2 Receptor. US patent 6,342,369 (Jan 29, 2002).
9. Ashkenazi, A. Fong, S., Goddard, A., Gurney, A., Napier, M., Tumas, D., Wood, W. A-33 polypeptides. US patent 6,410,708 (Jun 25, 2002).
10. Ashkenazi, A. APO-3 Receptor. US patent 6,462,176 B1 (Oct 8, 2002).
11. Ashkenazi, A. APO-2LI and APO-3 polypeptide antibodies. US patent 6,469,144 B1 (Oct 22, 2002).
12. Ashkenazi, A., Chamow, S. and Kogan, T. Carbohydrate-directed crosslinking reagents. US patent 6,582,928B1 (Jun 24, 2003).

Blast Result



NCBI

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

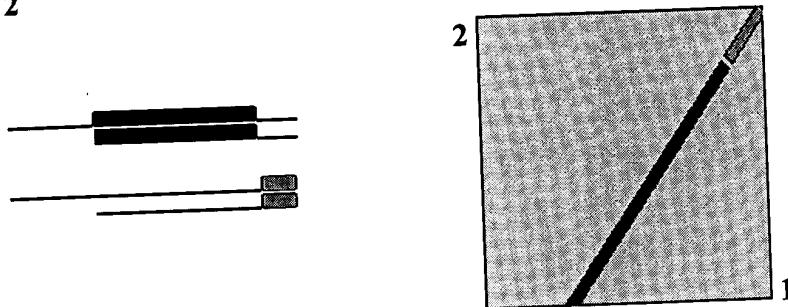
Blast 2 Sequences results

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.6 [Apr-09-2003]

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Sequence 1 gi 7243184 Homo sapiens mRNA for KIAA1402 protein, partial cds. Length 3970 (1 .. 3970)

Sequence 2 lcl|seq_2 Length 2789 (1 .. 2789)



NOTE: The statistics (bitscore and expect value) is calculated based on the size of nr database

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence

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 Identities = 2240/2243 (99%)
 Strand = Plus / Plus

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Blast Result

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NCBI Sequence Viewer



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REFERENCE 1 (sites)
 AUTHORS Nagase, T., Kikuno, R., Ishikawa, K.I., Hirosawa, M. and Ohara, O.
 TITLE Prediction of the coding sequences of unidentified human genes.
 XVI. The complete sequences of 150 new cDNA clones from brain which
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 (15-73 (2000))

JOURNAL DNA Res. 7 (1), 65-73 (2000)

20181126
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TITLE
JOURNAL
2 (bases 1 to 3970)
Ohara, O., Nagase, T. and Kikuno, R.
Direct Submission
Submitted (31-JAN-2000) Osamu Ohara, Kazusa DNA Research Institute,
Laboratory of DNA Technology; 1532-3 Yana, Kisarazu, Chiba
292-0812, Japan (E-mail:cdnainfo@kazusa.or.jp,
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